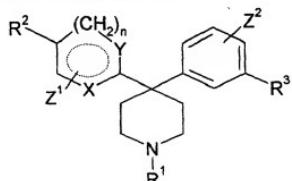


What is claimed is:

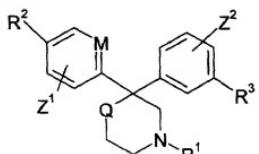
1. A method for treating a chemical dependency comprising administering an amount of a delta opioid receptor ligand and a serotonin reuptake inhibitor, said amounts being effective in said combination to treat said dependency, wherein said delta opioid receptor ligand is selected from the group consisting of:
- 5

a) a compound of the formula



10 and

b) a compound of the formula



wherein X and Y are selected, independently, from oxygen, nitrogen, sulfur and CH,
with the proviso that the ring in compound I containing X and Y must be aromatic and with the
15 proviso that X and Y cannot both be either oxygen or sulfur;

Q is oxygen or CH₂;

M is CH or N;

n is zero or one;

R¹ is hydrogen, (C₀-C₆)alkoxy-(C₀-C₆)alkyl-, wherein the total number of carbon atoms
20 is eight or less, aryl, aryl-(C₁-C₆)alkyl-, heteroaryl, heteroaryl-(C₁-C₆)alkyl-, heterocyclic,
heterocyclic-(C₁-C₆)alkyl, (C₃-C₇)cycloalkyl-, or (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl, wherein said
aryl and the aryl moiety of said aryl-(C₁-C₆)alkyl- are selected, independently, from phenyl and
naphthyl, and wherein said heteroaryl and the heteroaryl moiety of said heteroaryl-(C₁-C₆)alkyl- are selected,
25 independently, from pyrazinyl, benzofuranyl, quinolyl, isoquinolinyl, benzothienyl, isobenzofuryl,
pyrazolyl, indolyl, isoindolyl, benzimidazolyl, purinyl, carbazolyl,

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1,2,5-thiadiazolyl, quinazolinyl, pyridazinyl, pyrazinyl, cinnolinyl, phthalazinyl, quinoxalinyl, xanthinyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, oxazolyl, oxadiazolyl, isoxazolyl, thiazolyl, isothiazolyl, furanyl, pyrazolyl, pyrrolyl, tetrazolyl, triazolyl, thieryl, imidazolyl, 5-pyridinyl, and pyrimidinyl; and wherein said heterocyclic and the heterocyclic moiety of said heterocyclic-(C₁-C₆)alkyl- are selected from saturated or unsaturated nonaromatic monocyclic or bicyclic ring systems, wherein said monocyclic ring systems contain from four to seven ring carbon atoms, from one to three of which may optionally be replaced with O, N or S, and wherein said bicyclic ring systems contain from seven to twelve ring carbon atoms, from one to four of which may optionally be replaced with O, N or S; and wherein any of the aryl, heteroaryl or heterocyclic moieties of R¹ may optionally be substituted with from one to three substituents independently selected from halo, (C₁-C₆)alkyl optionally substituted with from one to seven fluorine atoms, phenyl, benzyl, hydroxy, acetyl, amino, cyano, nitro, (C₁-C₆)alkoxy, (C₁-C₆)alkylamino and [(C₁-C₆)alkyl]amino, and wherein any of alkyl moieties in R¹ may optionally be substituted with from one to seven fluorine atoms;

R² is hydrogen, aryl, halo, heteroaryl, heterocyclic, SO₂R⁴, COR⁴, CONR⁵R⁶, COOR⁴, or C(OH)R⁵R⁶ wherein each of R⁴, R⁵ and R⁶ is defined, independently, as R¹ is defined above, or R⁵ and R⁶, together with the carbon or nitrogen to which they are both attached, form a three to seven membered saturated ring containing from zero to three heteroatoms selected, independently, from O, N and S, and wherein said aryl, heteroaryl, and heterocyclic are defined as such terms are defined above in the definition of R¹, and wherein any of the aryl, heteroaryl and heterocyclic moieties of R² may optionally be substituted with from one to three substituents, independently selected from halo, (C₁-C₆)alkyl optionally substituted with from one to seven fluorine atoms, phenyl, benzyl, hydroxy, acetyl, amino, cyano, nitro, (C₁-C₆)alkoxy optionally substituted with from one to seven fluorine atoms, (C₁-C₆)alkylamino and [(C₁-C₆)alkyl]amino;

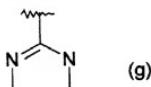
R³ is hydroxy, -(C₁-C₆)alkyl-OH, -OC(=O)R⁷, -(C₁-C₆)alkyl-(C₁-C₆)alkoxy, NHSO₂R⁷, C(OH)R⁷R⁸, halo, or heteroaryl as defined for R¹ above or CONHR⁷, wherein R⁷ and R⁸ are the same or different and are selected from hydrogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy and (C₁-C₄)alkoxy-(C₁-C₄)alkyl having a total of 4 or less carbon atoms, and wherein any of the alkyl moieties of R⁷ and R⁸ may optionally be substituted with from one to seven fluorine atoms; and

Z¹ and Z² are independently hydrogen, halo or (C₁-C₅)alkyl; with the proviso that there are no two adjacent ring oxygen atoms and no ring oxygen atom adjacent to either a ring nitrogen atom or a ring sulfur atom in any of the heterocyclic or heteroaryl moieties of formula I or II;

and the pharmaceutically acceptable salts of such compounds.

2. A method according to claim 1 wherein said delta opioid receptor ligand is a compound of the formula I wherein n is zero or one; X and Y are both nitrogen; R¹ is benzyl, cyclopropylmethyl, 2-pyridyl, 4-fluoro-2-pyridyl, pyrimidyl, 2-methylpentyl, 3-phenylpropyl, 2-ethoxyethyl or 3,5,5-trimethylhexyl; R² is CON(CH₂CH₃)₂, CON(CH₃)₂, CON(CH₂CH₃)CH₃, C(OH)(CH₃)₂, C(OH)(CH₂CH₃)₂, 3,3-dimethyloxazoline, 3,3-diethyloxazoline, benzoxazole, tetrazole or 3,5-dimethylpyrazole; and R³ is OH, CONH₂, fluoro, bromo, chloro, iodo, or NHSO₂R⁷.

3. A method according to claim 1 wherein said delta opioid receptor ligand is a compound of the formula I wherein n is zero or one; X is nitrogen and Y is CH or oxygen; R¹ is benzyl, cyclopropylmethyl, 2-pyridyl, 4-fluoro-2-pyridyl, pyrimidyl, 2-methylpentyl, 3-phenylpropyl, 2-ethoxyethyl, 3,5,5-trimethylhexyl, allyl, cyclopropylmethyl, methyl, 2,2,2-trifluoroethyl, methallyl, isopropyl, 2-pyridinyl, 2-pyrimidinyl, or

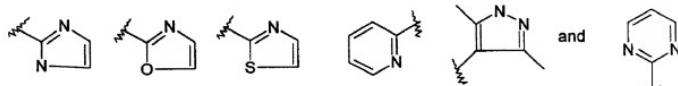


R² is CON(CH₂CH₃)₂, CON(CH₃)₂, CON(CH₂CH₃)CH₃, C(OH)(CH₃)₂, C(OH)(CH₂CH₃)₂, 3,3-dimethyloxazoline, 3,3-diethyloxazoline, benzoxazole, tetrazole or 3,5-dimethylpyrazole; and R³ is OH, CONH₂, fluoro, bromo, chloro, iodo, or NHSO₂R⁷.

4. A method according to claim 3 wherein n is zero, Y is CH, and R³ is OH or CONH₂.

5. A method according to claim 1 wherein said opioid receptor ligand is of the formula II wherein R¹ is cyclopropylmethyl, 3-cyclohexylpropyl, 2-phenylethyl, 2-methylpentyl, p-methylbenzyl, 2,2,2-trifluoroethyl, or 1-methylpentyl, R² is diethyl amide, methyl ethyl amide, a diethyl carbinol, tetrazole, or pyrazole, and R³ is hydroxy, fluoro, CONH₂, NHSO₂CH₃, or methoxy.

6. A method according to claim 1 wherein said opioid receptor ligand is of the formula II and Q is CH₂, X is CH, R³ is OH, CONH₂, or fluoro, R² is selected from C(OH)(C₂H₅)₂, CON(C₂H₅)₂, CONCH₃(C₂H₅) and the following cyclic groups:

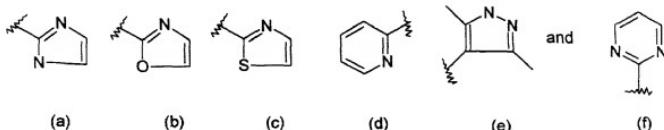


(a) (b) (c) (d) (e) (f)

and wherein Z¹ and Z² are selected, independently, from hydrogen and fluorine.

7. A method according to claim 1 wherein said opioid receptor ligand is selected from the group consisting of:

compounds of the formula II wherein Q is CH₂, M is N, R³ is OH, CONH₂, or fluoro, and R² is selected from C(OH)(C₂H₅)₂, CON(C₂H₅)₂ and one of cyclic groups (a) - (f):



5 compounds of the formula II wherein Q is oxygen, M is N, R³ is OH, CONH₂, or fluoro, and R² is selected from C(OH)(C₂H₅)₂, CON(C₂H₅)₂ and one of cyclic groups (a) - (f) depicted above;

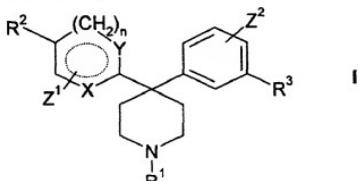
10 compounds of the formula II wherein Q is oxygen, M is CH, R³ is OH, CONH₂ or fluoro, Z¹ and Z² or selected, independently, from hydrogen and fluoro, and R¹ is selected from allyl, cyclopropylmethyl, methyl, methallyl, isopropyl, 2-pyridinyl, 2-pyrimidinyl and cyclic group (g) depicted above; and

15 8. A method according to claim 1 wherein said opioid receptor ligand is a compound of the formula II wherein Q is oxygen, M is N, R³ is OH, CONH₂ or fluoro, Z¹ and Z² or selected, independently, from hydrogen and fluoro, and R¹ is selected from allyl, cyclopropylmethyl, methyl, methallyl, isopropyl, 2-pyridinyl, 2-pyrimidinyl and cyclic group (g) depicted above.

9. A method of claim 1 wherein said serotonin reuptake ligand is selected from the group consisting of fluvoxamine, sertraline, citalopram, fluoxetine, paroxetine, imipramine, zimelidine, vanlafaxine, and nefazodone.

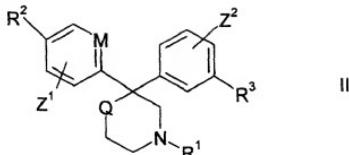
20 10. A pharmaceutical composition for the treatment of a chemical dependency wherein composition comprises amounts of a delta opioid receptor ligand and a serotonin reuptake inhibitor, said amounts being effective in said combination to treat said dependency, wherein said delta opioid receptor ligand is selected from the group consisting of

a) a compound of the formula



and

b) a compound of the formula



5 wherein X and Y are selected, independently, from oxygen, nitrogen, sulfur and CH,
with the proviso that the ring in compound I containing X and Y must be aromatic and with the
proviso that X and Y cannot both be either oxygen or sulfur;

Q is oxygen or CH₂;

M is CH or N;

10 n is zero or one;

R¹ is hydrogen, (C₀-C₆)alkoxy-(C₀-C₆)alkyl-, wherein the total number of carbon atoms
is eight or less, aryl, aryl-(C₁-C₆)alkyl-, heteroaryl, heteroaryl-(C₁-C₆)alkyl-, heterocyclic,
heterocyclic-(C₁-C₆)alkyl, (C₃-C₇)cycloalkyl-, or (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl, wherein said
aryl and the aryl moiety of said aryl-(C₁-C₆)alkyl- are selected, independently, from phenyl and
15 naphthyl, and wherein said heteroaryl and the heteroaryl moiety of said heteroaryl-(C₁-
C₆)alkyl- are selected, independently, from pyrazinyl, benzofuranyl, quinolyl, isoquinolyl,
benzothienyl, isobenzofuryl, pyrazolyl, indolyl, isoindolyl, benzimidazolyl, purinyl, carbazolyl,
1,2,5-thiadiazolyl, quinazolinyl, pyridazinyl, pyrazinyl, cinnolinyl, phthalazinyl, quinoxalinyl,
xanthinyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl,
20 imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, oxazolyl, oxadiazolyl, isoxazolyl,
thiazolyl, isothiazolyl, furanyl, pyrazolyl, pyrrolyl, tetrazolyl, triazolyl, thienyl, imidazolyl,
pyridinyl, and pyrimidinyl; and wherein said heterocyclic and the heterocyclic moiety of said
heterocyclic-(C₁-C₆)alkyl- are selected from saturated or unsaturated nonaromatic monocyclic
or bicyclic ring systems, wherein said monocyclic ring systems contain from four to seven ring
25 carbon atoms, from one to three of which may optionally be replaced with O, N or S, and
wherein said bicyclic ring systems contain from seven to twelve ring carbon atoms, from one
to four of which may optionally be replaced with O, N or S; and wherein any of the aryl,
heteroaryl or heterocyclic moieties of R¹ may optionally be substituted with from one to three
substituents independently selected from halo, (C₁-C₆)alkyl optionally substituted with from one to
30 seven fluorine atoms, phenyl, benzyl, hydroxy, acetyl, amino, cyano, nitro, (C₁-C₆)alkoxy, (C₁-
C₆)alkylamino and [(C₁-C₆)alkyl]₂amino, and wherein any of alkyl moieties in R¹ may optionally be
substituted with from one to seven fluorine atoms;

- R² is hydrogen, aryl, halo, heteroaryl, heterocyclic, SO₂R⁴, COR⁴, CONR⁵R⁶, COOR⁴, or C(OH)R⁵R⁶ wherein each of R⁴, R⁵ and R⁶ is defined, independently, as R¹ is defined above, or R⁵ and R⁶, together with the carbon or nitrogen to which they are both attached, form a three to seven membered saturated ring containing from zero to three heterocarbons selected, independently, from O, N and S, and wherein said aryl, heteroaryl, and heterocyclic are defined as such terms are defined above in the definition of R¹, and wherein any of the aryl, heteroaryl and heterocyclic moieties of R² may optionally be substituted with from one to three substituents, independently selected from halo, (C₁-C₆)alkyl optionally substituted with from one to seven fluorine atoms, phenyl, benzyl, hydroxy, acetyl, amino, cyano, nitro, (C₁-C₆)alkoxy 10 optionally substituted with from one to seven fluorine atoms, (C₁-C₆)alkylamino and [(C₁-C₆)alkyl]₂amino;
- R³ is hydroxy, -(C₁-C₆)alkyl-OH, -OC(=O)R⁷, -(C₁-C₆)alkyl-(C₁-C₆)alkoxy, NHSO₂R⁷, C(OH)R⁷R⁸, halo, or heteroaryl as defined for R¹ above or CONHR⁷, wherein R⁷ and R⁸ are the same or different and are selected from hydrogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy and (C₁-15 C₄)alkoxy-(C₁-C₄)alkyl having a total of 4 or less carbon atoms, and wherein any of the alkyl moieties of R⁷ and R⁸ may optionally be substituted with from one to seven fluorine atoms; and
- Z¹ and Z² are independently hydrogen, halo or (C₁-C₆)alkyl;
with the proviso that there are no two adjacent ring oxygen atoms and no ring oxygen atom adjacent to either a ring nitrogen atom or a ring sulfur atom in any of the heterocyclic or heteroaryl moieties of formula I;
- and the pharmaceutically acceptable salts of such compounds.

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